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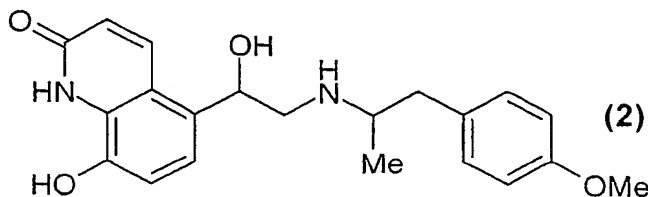
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(54) Title: **MEDICAMENTS FOR INHALATION COMPRISING STEROIDS AND A BETAMIMETIC**

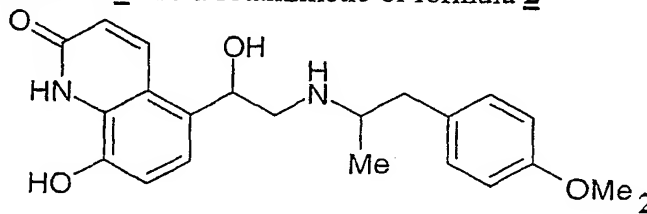


(57) Abstract: The present invention relates to novel pharmaceutical compositions comprising one or more, preferably one steroid I and a betamimetic of Formula (2) processes for preparing them and their use in the treatment of respiratory complaints.

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## MEDICAMENTS FOR INHALATION COMPRISING STEROIDS AND A BETAMIMETIC

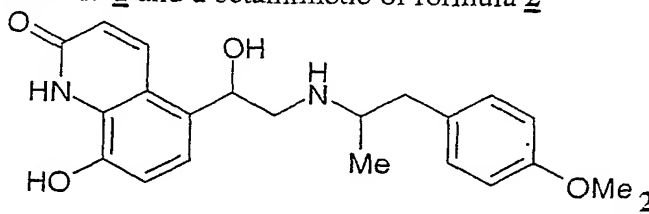
The present invention relates to novel pharmaceutical compositions comprising one or more, preferably one steroid 1 and a betamimetic of formula 2



processes for preparing them and their use in the treatment of respiratory complaints.

### Description of the invention

The present invention relates to novel pharmaceutical compositions comprising one or more, preferably one steroid 1 and a betamimetic of formula 2



optionally in the form of its diastereomers, mixtures of its diastereomers, racemats or physiologically acceptable acid addition salts thereof, and optionally in form of the hydrates or solvates thereof, and optionally together with a pharmaceutically acceptable excipient.

15

Examples of pharmacologically acceptable acid addition salts of the betamimetic 2 according to the invention are the pharmaceutically acceptable salts which are selected from among the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, 1-hydroxy-2-naphthalenecarboxylic acid, 4-phenylcinnamic acid or maleic acid. If desired, mixtures of the abovementioned acids may also be used to prepare the salts of 2.

20

According to the invention, the salts of 2 selected from among the hydrochloride, hydrobromide, sulphate, phosphate, fumarate, methanesulphonate, maleate and xinafoate are preferred. Particularly preferred is the hydrochloric acid salt of 2.

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Surprisingly, an unexpectedly beneficial therapeutic effect can be observed in the treatment of inflammatory and/or obstructive diseases of the respiratory tract if the betamimetic of formula 2 is used with one or more steroids 1.

- 5 The beneficial therapeutic effect mentioned above may be observed both when the two active substances are administered simultaneously in a single active substance formulation and when they are administered successively in separate formulations. According to the invention, it is preferable to administer the two active substance ingredients simultaneously in a single formulation.

10

According to the instant invention preferred steroids 1 which are optionally also referred to as corticosteroids, denote compounds selected from among methyl prednisolone, prednisone, butixocort propionate, RPR-106541, flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide, ST-126, dexamethasone, 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid (S)-fluoromethyl ester, and 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-17 $\alpha$ -propionyloxy-androsta-1,4-diene-17 $\beta$ -carbothioic acid (S)-(2-oxo-tetrahydro-furan-3S-yl) ester.

15

- 20 Preferably, the compound 1 is selected from among flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide, ST-126, dexamethasone, 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid (S)-fluoromethyl ester, and 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-17 $\alpha$ -propionyloxy-androsta-1,4-diene-17 $\beta$ -carbothioic acid (S)-(2-oxo-tetrahydro-furan-3S-yl) ester. More preferably, the compound 1 is selected from among budesonide, fluticasone, mometasone, ciclesonide, and 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid (S)-fluoromethyl ester.

25

- 30 Exemplary preferred combinations are for instance: a) 2-hydrochloride and budesonide; b) 2-hydrochloride and fluticasone, in particular fluticasone propionate ester; c) 2-hydrochloride and mometasone, for instance as the furoate ester; d) 2-hydrochloride and ciclesonide; e) 2-hydrochloride and 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid (S)-fluoromethyl ester; f) 2-hydrochloride and 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-17 $\alpha$ -

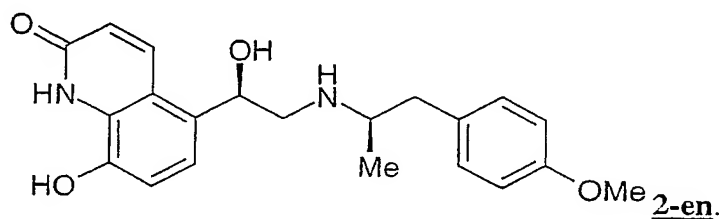
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propionyloxy-androsta-1,4-diene-17 $\beta$ -carbothioic acid (S)-(2-oxo-tetrahydro-furan-3S-yl) ester.

In the pharmaceutical compositions according to the invention, the compound 2 may be present in the form of its racemates, enantiomers or mixtures thereof. The separation of the enantiomers from the racemates may be carried out using methods known in the art (e.g. by chromatography on chiral phases, etc.) If the compounds 2 are used in the form of their enantiomers, it is particularly preferable to use the enantiomers possessing R-configuration at the C-OH group.

10

Of particular interest within the scope of the instant invention is the R,R-enantiomer of formula 2-en



15 Within the scope of the present invention the betamimetic 2 may possibly also be referred to as sympathomimetic or beta<sub>2</sub>-agonist ( $\beta_2$ -agonist). All these terms are to be regarded as interchangeable for the purposes of the present invention.

Any reference to steroids 1 within the scope of the present invention includes a reference to the salts or derivatives which may be formed from the steroids. Examples of possible salts or derivatives include: sodium salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates. In some cases the compounds of formula 1 may also occur in the form of their hydrates. Any reference to steroids 1 within the scope of the present invention also includes a reference to the compounds 1 in the form of their diastereomers, mixtures of diastereomers or in the form of the racemates.

In one aspect the present invention relates to the abovementioned pharmaceutical compositions which contain, in addition to therapeutically effective quantities of 1 and 2, a pharmaceutically acceptable carrier. In another aspect the present invention relates to the abovementioned pharmaceutical compositions which do not contain any pharmaceutically acceptable carrier in addition to therapeutically effective quantities of 1 and 2.

The present invention also relates to the use of therapeutically effective quantities of the compound of formula 2 for preparing a pharmaceutical composition also containing steroids 1 for treating inflammatory or obstructive diseases of the respiratory tract.

5 Preferably, the present invention relates to the abovementioned use for preparing a pharmaceutical composition for treating asthma or COPD.

Within the scope of the present invention the compounds 1 and 2 may be administered simultaneously or successively, while it is preferable according to the invention to  
10 administer compounds 1 and 2 simultaneously.

The present invention further relates to the use of therapeutically effect amounts of the compound of formula 2 and steroids 1 for treating inflammatory or obstructive respiratory complaints, particularly asthma or COPD.

15

The proportions in which the active substances 1 and 2 may be used in the active substance combinations according to the invention are variable. Active substances 1 and 2 may possibly be present in the form of their solvates or hydrates. Depending on the choice of the compounds 1 and 2, the weight ratios which may be used within the scope of the  
20 present invention vary on the basis of the different molecular weights of the various compounds and their different potencies.

As a rule, the pharmaceutical combinations according to the invention may contain the steroid 1 and compound 2 in ratios by weight ranging from 1:250 to 250:1, preferably from  
25 1:150 to 150:1. In the particularly preferred pharmaceutical combinations which contain in addition to 2 a compound selected for instance from among the group consisting of budesonide, fluticasone, mometasone, and ciclesonide as the steroid 1, the weight ratios of 2 to 1 are most preferably in a range from about 1:70 to 30:1, more preferably from 1:35 to 15:1.

30

For example and without limiting the scope of the invention, the combination of active substances according to the invention may contain in the case of the most preferred steroids 1 budesonide, fluticasone, mometasone, and ciclesonide the steroid and the compound of formula 2 (based on free base) for example in the following ratios by weight:  
35 1:15, 1:14, 1:13, 1:12, 1:11, 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1,

6:1, 7:1, 8:1, 9:1, 10:1, 11:1, 12:1, 13:1, 14:1, 15:1, 16:1, 17:1, 18:1, 19:1, 20:1, 21:1, 22:1, 23:1, 24:1, 25:1, 26:1, 27:1, 28:1, 29:1, 30:1, 31:1, 32:1, 33:1, 34:1, 35:1.

The pharmaceutical compositions according to the invention containing the combinations of 1 and 2 are in particular in case of budesonide, fluticasone, mometasone or ciclesonide as the steroid 1, preferably administered so that the steroid 1 and 2 (values based on free base) are present together in dosages of 10 to 2000 $\mu$ g, more preferably from 15 to 1000 $\mu$ g, even more preferably from 20 to 800 $\mu$ g, and preferably according to the invention from 30 to 750 $\mu$ g, preferably from 40 to 700 $\mu$ g per single dose.

For example, combinations of 1 and 2 according to the invention contain an amount of 1 and 2 (values based on free base) such that the total dosage per single dose is about 15 $\mu$ g, 20 $\mu$ g, 25 $\mu$ g, 30 $\mu$ g, 35 $\mu$ g, 45 $\mu$ g, 50 $\mu$ g, 55 $\mu$ g, 60 $\mu$ g, 65 $\mu$ g, 70 $\mu$ g, 75 $\mu$ g, 80 $\mu$ g, 85 $\mu$ g, 90 $\mu$ g, 95 $\mu$ g, 100 $\mu$ g, 105 $\mu$ g, 110 $\mu$ g, 115 $\mu$ g, 120 $\mu$ g, 125 $\mu$ g, 130 $\mu$ g, 135 $\mu$ g, 140 $\mu$ g, 145 $\mu$ g, 150 $\mu$ g, 155 $\mu$ g, 160 $\mu$ g, 165 $\mu$ g, 170 $\mu$ g, 175 $\mu$ g, 180 $\mu$ g, 185 $\mu$ g, 190 $\mu$ g, 195 $\mu$ g, 200 $\mu$ g, 205 $\mu$ g, 210 $\mu$ g, 215 $\mu$ g, 220 $\mu$ g, 225 $\mu$ g, 230 $\mu$ g, 235 $\mu$ g, 240 $\mu$ g, 245 $\mu$ g, 250 $\mu$ g, 255 $\mu$ g, 260 $\mu$ g, 265 $\mu$ g, 270 $\mu$ g, 275 $\mu$ g, 280 $\mu$ g, 285 $\mu$ g, 290 $\mu$ g, 295 $\mu$ g, 300 $\mu$ g, 305 $\mu$ g, 310 $\mu$ g, 315 $\mu$ g, 320 $\mu$ g, 325 $\mu$ g, 330 $\mu$ g, 335 $\mu$ g, 340 $\mu$ g, 345 $\mu$ g, 350 $\mu$ g, 355 $\mu$ g, 360 $\mu$ g, 365 $\mu$ g, 370 $\mu$ g, 375 $\mu$ g, 380 $\mu$ g, 385 $\mu$ g, 390 $\mu$ g, 395 $\mu$ g, 400 $\mu$ g, 405 $\mu$ g, 410 $\mu$ g, 415 $\mu$ g, 420 $\mu$ g, 425 $\mu$ g, 430 $\mu$ g, 435 $\mu$ g, 440 $\mu$ g, 445 $\mu$ g, 450 $\mu$ g, 455 $\mu$ g, 460 $\mu$ g, 465 $\mu$ g, 470 $\mu$ g, 475 $\mu$ g, 480 $\mu$ g, 485 $\mu$ g, 490 $\mu$ g, 495 $\mu$ g, 500 $\mu$ g, 505 $\mu$ g, 510 $\mu$ g, 515 $\mu$ g, 520 $\mu$ g, 525 $\mu$ g, 530 $\mu$ g, 535 $\mu$ g, 540 $\mu$ g, 545 $\mu$ g, 550 $\mu$ g, 555 $\mu$ g, 560 $\mu$ g, 565 $\mu$ g, 570 $\mu$ g, 575 $\mu$ g, 580 $\mu$ g, 585 $\mu$ g, 590 $\mu$ g, 595 $\mu$ g, 600 $\mu$ g, 605 $\mu$ g, 610 $\mu$ g, 615 $\mu$ g, 620 $\mu$ g, 625 $\mu$ g, 630 $\mu$ g, 635 $\mu$ g, 640 $\mu$ g, 645 $\mu$ g, 650 $\mu$ g, 655 $\mu$ g, 660 $\mu$ g, 665 $\mu$ g, 670 $\mu$ g, 675 $\mu$ g, 680 $\mu$ g, 685 $\mu$ g, 690 $\mu$ g, 695 $\mu$ g, 700 $\mu$ g or similar. It is clear to anyone skilled in the art that the suggested dosages per single dose specified above are not to be regarded as being limited to the numerical values actually stated. Fluctuations of about  $\pm 2.5$   $\mu$ g, particularly in the decimal range, are also included, as will be apparent to the skilled man. In these dosage ranges, the active substances 1 and 2 may be present in the weight ratios given above.

For example, without restricting the scope of the invention thereto, the combinations of 1 and 2 according to the invention may in particular in the case of budesonide, fluticasone, mometasone or ciclesonide contain a quantity of steroid 1 and 2 (values based on free base) such that, for each single dose, 25 $\mu$ g of 1 and 5 $\mu$ g of 2, 25 $\mu$ g of 1 and 10 $\mu$ g of 2, 25 $\mu$ g of 1 and 15 $\mu$ g of 2, 25 $\mu$ g of 1 and 25 $\mu$ g of 2, 25 $\mu$ g of 1 and 50 $\mu$ g of 2, 25 $\mu$ g of 1 and

100µg of 2, 50µg of 1 and 5µg of 2, 50µg of 1 and 10µg of 2, 50µg of 1 and 15µg of 2,  
50µg of 1 and 25µg of 2, 50µg of 1 and 50µg of 2, 50µg of 1 and 100µg of 2, 75µg of 1  
and 5µg of 2, 75µg of 1 and 10µg of 2, 75µg of 1 and 15µg of 2, 75µg of 1 and 25µg of 2,  
75µg of 1 and 50µg of 2, 75µg of 1 and 100µg of 2, 100µg of 1 and 5µg of 2, 100µg of 1  
5 and 10µg of 2, 100µg of 1 and 15µg of 2, 100µg of 1 and 25µg of 2, 100µg of 1 and 50µg  
of 2, 100µg of 1 and 100µg of 2, 125µg of 1 and 5µg of 2, 125µg of 1 and 10µg of 2,  
125µg of 1 and 15µg of 2, 125µg of 1 and 25µg of 2, 125µg of 1 and 50µg of 2, 125µg of  
1 and 100µg of 2, 150µg of 1 and 5µg of 2, 150µg of 1 and 10µg of 2, 150µg of 1 and  
15µg of 2, 150µg of 1 and 25µg of 2, 150µg of 1 and 50µg of 2, 150µg of 1 and 100µg of  
10 2, 175µg of 1 and 5µg of 2, 175µg of 1 and 10µg of 2, 175µg of 1 and 15µg of 2, 175µg of  
1 and 25µg of 2, 175µg of 1 and 50µg of 2, 175µg of 1 and 100µg of 2, 200µg of 1 and  
5µg of 2, 200µg of 1 and 10µg of 2, 200µg of 1 and 15µg of 2, 200µg of 1 and 25µg of 2,  
200µg of 1 and 50µg of 2, 200µg of 1 and 100µg of 2, 250µg of 1 and 5µg of 2, 250µg of  
1 and 10µg of 2, 250µg of 1 and 15µg of 2, 250µg of 1 and 25µg of 2, 250µg of 1 and  
15 50µg of 2, 250µg of 1 and 100µg of 2 are present, for example.

From the aforementioned examples for suitable doses of the 1 and 2 containing combinations according to the invention, the corresponding amounts of the preferably used acid addition salts of 2 are readily calculable.

20

The active substance combinations of 1 and 2 according to the invention are preferably administered by inhalation. For this purpose, ingredients 1 and 2 have to be made available in forms suitable for inhalation. Inhalable preparations according to the invention include inhalable powders, propellant-containing metered dose aerosols or  
25 propellant-free inhalable solutions. Inhalable powders according to the invention containing the combination of active substances 1 and 2 may consist of the active substances on their own or of a mixture of the active substances with physiologically acceptable excipients. Within the scope of the present invention, the term carrier may optionally be used instead of the term excipient. Within the scope of the present invention,  
30 the term propellant-free inhalable solutions also includes concentrates or sterile inhalable solutions ready for use. The preparations according to the invention may contain the combination of active substances 1 and 2 either together in one formulation or in two separate formulations. These formulations which may be used within the scope of the present invention are described in more detail in the next part of the specification.

35

**A) Inhalable powder containing the combinations of active substances 1 and 2 according to the invention:**

The inhalable powders according to the invention may contain 1 and 2 either on their own or in admixture with suitable physiologically acceptable excipients.

5 If the active substances 1 and 2 are present in admixture with physiologically acceptable excipients, the following physiologically acceptable excipients may be used to prepare these inhalable powders according to the invention: monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose, trehalose), oligo- and polysaccharides (e.g. dextran), polyalcohols (e.g. sorbitol, mannitol, xylitol),  
10 cyclodextrines (e.g.  $\alpha$ -cyclodextrine,  $\beta$ -cyclodextrine,  $\chi$ -cyclodextrine, methyl- $\beta$ -cyclodextrine, hydroxypropyl- $\beta$ -cyclodextrine), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose, trehalose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates.

15 Within the scope of the inhalable powders according to the invention the excipients have a maximum average particle size of up to  $250\mu\text{m}$ , preferably between 10 and  $150\mu\text{m}$ , most preferably between 15 and  $80\mu\text{m}$ . It may sometimes seem appropriate to add finer excipient fractions with an average particle size of 1 to  $9\mu\text{m}$  to the excipient mentioned  
20 above. These finer excipients are also selected from the group of possible excipients listed hereinbefore. Finally, in order to prepare the inhalable powders according to the invention, micronised active substance 1 and 2, preferably with an average particle size of 0.5 to  $10\mu\text{m}$ , more preferably from 1 to  $6\mu\text{m}$ , is added to the excipient mixture. Processes for producing the inhalable powders according to the invention by grinding and micronising  
25 and by finally mixing the ingredients together are known from the prior art. The inhalable powders according to the invention may be prepared and administered either in the form of a single powder mixture which contains both 1 and 2 or in the form of separate inhalable powders which contain only 1 or 2.

30 The inhalable powders according to the invention may be administered using inhalers known from the prior art. Inhalable powders according to the invention which contain one or more physiologically acceptable excipients in addition to 1 and 2 may be administered, for example, by means of inhalers which deliver a single dose from a supply using a measuring chamber as described in US 4570630A, or by other means as described in  
35 DE 36 25 685 A. The inhalable powders according to the invention which contain 1 and 2



optionally in conjunction with a physiologically acceptable excipient may be administered, for example, using the inhaler known by the name Turbuhaler® or using inhalers as disclosed for example in EP 237507 A. Preferably, the inhalable powders according to the invention which contain physiologically acceptable excipient in addition to 1 and 2 are  
5 packed into capsules (to produce so-called inhalettes) which are used in inhalers as described, for example, in WO 94/28958.

A particularly preferred inhaler for using the pharmaceutical combination according to the invention in inhalettes is shown in Figure 1.  
10 This inhaler (Handyhaler) for inhaling powdered pharmaceutical compositions from capsules is characterised by a housing 1 containing two windows 2, a deck 3 in which there are air inlet ports and which is provided with a screen 5 secured via a screen housing 4, an inhalation chamber 6 connected to the deck 3 on which there is a push button 9 provided with two sharpened pins 7 and movable counter to a spring 8, and a mouthpiece 12 which  
15 is connected to the housing 1, the deck 3 and a cover 11 via a spindle 10 to enable it to be flipped open or shut, as well as airholes 13 for adjusting the flow resistance.

If the inhalable powders according to the invention are packed into capsules (inhalers) for the preferred use described above, the quantities packed into each capsule should be 1 to  
20 30mg per capsule. These capsules contain, according to the invention, either together or separately, the doses of 1 and 2 mentioned hereinbefore for each single dose.

**B) Propellant gas-driven inhalation aerosols containing the combinations of active substances 1 and 2:**

25 Inhalation aerosols containing propellant gas according to the invention may contain substances 1 and 2 dissolved in the propellant gas or in dispersed form. 1 and 2 may be present in separate formulations or in a single preparation, in which 1 and 2 are either both dissolved, both dispersed or only one component is dissolved and the other is dispersed. The propellant gases which may be used to prepare the inhalation aerosols according to the  
30 invention are known from the prior art. Suitable propellant gases are selected from among hydrocarbons such as n-propane, n-butane or isobutane and halohydrocarbons such as fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The propellant gases mentioned above may be used on their own or in mixtures thereof. Particularly preferred propellant gases are halogenated alkane derivatives selected from  
35 TG11, TG12, TG134a (1,1,1,2-tetrafluoroethane) and TG227 (1,1,1,2,3,3,3-

heptafluoropropane) and mixtures thereof, of which the propellant gases TG134a, TG227 and mixtures thereof are preferred.

5 The propellant-driven inhalation aerosols according to the invention may also contain other ingredients such as co-solvents, stabilisers, surfactants, antioxidants, lubricants and pH adjusters. All these ingredients are known in the art.

10 The inhalation aerosols containing propellant gas according to the invention may contain up to 5 wt.-% of active substance 1 and/or 2. Aerosols according to the invention contain, for example, 0.002 to 5 wt.-%, 0.01 to 3 wt.-%, 0.015 to 2 wt.-%, 0.1 to 2 wt.-%, 0.5 to 2 wt.-% or 0.5 to 1 wt.-% of active substance 1 and/or 2.

15 If the active substances 1 and/or 2 are present in dispersed form, the particles of active substance preferably have an average particle size of up to 10µm, preferably from 0.1 to 6µm, more preferably from 1 to 5µm.

The propellant-driven inhalation aerosols according to the invention mentioned above may be administered using inhalers known in the art (MDIs = metered dose inhalers). Accordingly, in another aspect, the present invention relates to pharmaceutical  
20 compositions in the form of propellant-driven aerosols as hereinbefore described combined with one or more inhalers suitable for administering these aerosols. In addition, the present invention relates to inhalers which are characterised in that they contain the propellant gas-containing aerosols described above according to the invention. The present invention also relates to cartridges fitted with a suitable valve which can be used in a suitable inhaler and  
25 which contain one of the above-mentioned propellant gas-containing inhalation aerosols according to the invention. Suitable cartridges and methods of filling these cartridges with the inhalable aerosols containing propellant gas according to the invention are known from the prior art.

30 **C) Propellant-free inhalable solutions or suspensions containing the combinations of active substances 1 and 2 according to the invention:**

Propellant-free inhalable solutions and suspensions according to the invention contain, for example, aqueous or alcoholic, preferably ethanolic solvents, optionally ethanolic solvents mixed with aqueous solvents. If aqueous/ethanolic solvent mixtures are used the relative  
35 proportion of ethanol compared with water is not limited but preferably the maximum is up

to 70 percent by volume, more particularly up to 60 percent by volume of ethanol. The remainder of the volume is made up of water. The solutions or suspensions containing 1 and 2, separately or together, are adjusted to a pH of 2 to 7, preferably 2 to 5, using suitable acids. The pH may be adjusted using acids selected from inorganic or organic acids. Examples of particularly suitable inorganic acids include hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid and/or phosphoric acid. Examples of particularly suitable organic acids include ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and/or propionic acid etc. Preferred inorganic acids are hydrochloric and sulphuric acids. It is also possible to use the acids which have already formed an acid addition salt with one of the active substances. Of the organic acids, ascorbic acid, fumaric acid and citric acid are preferred. If desired, mixtures of the above acids may be used, particularly in the case of acids which have other properties in addition to their acidifying qualities, e.g. as flavourings, antioxidants or complexing agents, such as citric acid or ascorbic acid, for example. According to the invention, it is particularly preferred to use hydrochloric acid to adjust the pH.

According to the invention, the addition of editic acid (EDTA) or one of the known salts thereof, sodium editate, as stabiliser or complexing agent is unnecessary in the present formulation. Other embodiments may contain this compound or these compounds. In a preferred embodiment the content based on sodium editate is less than 100mg/100ml, preferably less than 50mg/100 ml, more preferably less than 20mg/100 ml. Generally, inhalable solutions in which the content of sodium editate is from 0 to 10mg/100ml are preferred.

Co-solvents and/or other excipients may be added to the propellant-free inhalable solutions according to the invention. Preferred co-solvents are those which contain hydroxyl groups or other polar groups, e.g. alcohols - particularly isopropyl alcohol, glycols - particularly propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters. The terms excipients and additives in this context denote any pharmacologically acceptable substance which is not an active substance but which can be formulated with the active substance or substances in the pharmacologically suitable solvent in order to improve the qualitative properties of the active substance formulation. Preferably, these substances have no pharmacological effect or, in connection with the desired therapy, no appreciable or at least no undesirable

pharmacological effect. The excipients and additives include, for example, surfactants such as soya lecithin, oleic acid, sorbitan esters, such as polysorbates, polyvinylpyrrolidone, other stabilisers, complexing agents, antioxidants and/or preservatives which guarantee or prolong the shelf life of the finished pharmaceutical  
5 formulation, flavourings, vitamins and/or other additives known in the art. The additives also include pharmacologically acceptable salts such as sodium chloride as isotonic agents. The preferred excipients include antioxidants such as ascorbic acid, for example, provided that it has not already been used to adjust the pH, vitamin A, vitamin E, tocopherols and similar vitamins and provitamins occurring in the human body.

10

Preservatives may be used to protect the formulation from contamination with pathogens. Suitable preservatives are those which are known in the art, particularly cetyl pyridinium chloride, benzalkonium chloride or benzoic acid or benzoates such as sodium benzoate in the concentration known from the prior art. The preservatives mentioned above are  
15 preferably present in concentrations of up to 50mg/100ml, more preferably between 5 and 20mg/100ml.

Preferred formulations contain, in addition to the solvent water and the combination of active substances 1 and 2, only benzalkonium chloride and sodium editate. In another  
20 preferred embodiment, no sodium editate is present.

The propellant-free inhalable solutions according to the invention are administered in particular using inhalers of the kind which are capable of nebulising a small amount of a liquid formulation in the therapeutic dose within a few seconds to produce an aerosol  
25 suitable for therapeutic inhalation. Within the scope of the present invention, preferred inhalers are those in which a quantity of less than 100 $\mu$ L, preferably less than 50 $\mu$ L, more preferably between 20 and 30 $\mu$ L of active substance solution can be nebulised in preferably one spray action to form an aerosol with an average particle size of less than 20 $\mu$ m, preferably less than 10 $\mu$ m, in such a way that the inhalable part of the aerosol  
30 corresponds to the therapeutically effective quantity.

An apparatus of this kind for propellant-free delivery of a metered quantity of a liquid pharmaceutical composition for inhalation is described for example in International Patent Application WO 91/14468 and also in WO 97/12687 (cf. in particular Figures 6a and 6b).  
35 The nebulisers (devices) described therein are known by the name Respimat®.

This nebuliser (Respimat®) can advantageously be used to produce the inhalable aerosols according to the invention containing the combination of active substances 1 and 2.

Because of its cylindrical shape and handy size of less than 9 to 15 cm long and 2 to 4 cm wide, this device can be carried at all times by the patient. The nebuliser sprays a defined  
5 volume of pharmaceutical formulation using high pressures through small nozzles so as to produce inhalable aerosols.

The preferred atomiser essentially consists of an upper housing part, a pump housing, a nozzle, a locking mechanism, a spring housing, a spring and a storage container,  
10 characterised by

- a pump housing which is secured in the upper housing part and which comprises at one end a nozzle body with the nozzle or nozzle arrangement,
  - a hollow plunger with valve body,
  - a power takeoff flange in which the hollow plunger is secured and which is located  
15 in the upper housing part,
  - a locking mechanism situated in the upper housing part,
  - a spring housing with the spring contained therein, which is rotatably mounted on the upper housing part by means of a rotary bearing,
  - a lower housing part which is fitted onto the spring housing in the axial direction.
- 20

The hollow plunger with valve body corresponds to a device disclosed in WO 97/12687. It projects partially into the cylinder of the pump housing and is axially movable within the cylinder. Reference is made in particular to Figures 1 to 4, especially Figure 3, and the relevant parts of the description. The hollow plunger with valve body exerts a pressure of  
25 5 to 60 Mpa (about 50 to 600 bar), preferably 10 to 60 Mpa (about 100 to 600 bar) on the fluid, the measured amount of active substance solution, at its high pressure end at the moment when the spring is actuated. Volumes of 10 to 50 microlitres are preferred, while volumes of 10 to 20 microlitres are particularly preferred and a volume of 15 microlitres per spray is most particularly preferred.

30

The valve body is preferably mounted at the end of the hollow plunger facing the valve body.

The nozzle in the nozzle body is preferably microstructured, i.e. produced by  
35 microtechnology. Microstructured nozzle bodies are disclosed for example in WO

94/07607; reference is hereby made to the contents of this specification, particularly Figure 1 therein and the associated description.

The nozzle body consists for example of two sheets of glass and/or silicon firmly joined together, at least one of which has one or more microstructured channels which connect the  
5 nozzle inlet end to the nozzle outlet end. At the nozzle outlet end there is at least one round or non-round opening 2 to 10 microns deep and 5 to 15 microns wide, the depth preferably being 4.5 to 6.5 microns while the length is preferably 7 to 9 microns.

In the case of a plurality of nozzle openings, preferably two, the directions of spraying of the nozzles in the nozzle body may extend parallel to one another or may be inclined  
10 relative to one another in the direction of the nozzle opening. In a nozzle body with at least two nozzle openings at the outlet end the directions of spraying may be at an angle of 20 to 160° to one another, preferably 60 to 150°, most preferably 80 to 100°. The nozzle openings are preferably arranged at a spacing of 10 to 200 microns, more preferably at a spacing of 10 to 100 microns, most preferably 30 to 70 microns. Spacings of 50 microns  
15 are most preferred. The directions of spraying will therefore meet in the vicinity of the nozzle openings.

The liquid pharmaceutical preparation strikes the nozzle body with an entry pressure of up to 600 bar, preferably 200 to 300 bar, and is atomised into an inhalable aerosol through the nozzle openings. The preferred particle or droplet sizes of the aerosol are up to 20  
20 microns, preferably 3 to 10 microns.

The locking mechanism contains a spring, preferably a cylindrical helical compression spring, as a store for the mechanical energy. The spring acts on the power takeoff flange as an actuating member the movement of which is determined by the position of a locking  
25 member. The travel of the power takeoff flange is precisely limited by an upper and lower stop. The spring is preferably biased, via a power step-up gear, e.g. a helical thrust gear, by an external torque which is produced when the upper housing part is rotated counter to the spring housing in the lower housing part. In this case, the upper housing part and the power takeoff flange have a single or multiple V-shaped gear.

30 The locking member with engaging locking surfaces is arranged in a ring around the power takeoff flange. It consists, for example, of a ring of plastic or metal which is inherently radially elastically deformable. The ring is arranged in a plane at right angles to the atomiser axis. After the biasing of the spring, the locking surfaces of the locking member  
35 move into the path of the power takeoff flange and prevent the spring from relaxing. The

locking member is actuated by means of a button. The actuating button is connected or coupled to the locking member. In order to actuate the locking mechanism, the actuating button is moved parallel to the annular plane, preferably into the atomiser; this causes the deformable ring to deform in the annular plane. Details of the construction of the locking mechanism are given in WO 97/20590.

The lower housing part is pushed axially over the spring housing and covers the mounting, the drive of the spindle and the storage container for the fluid.

When the atomiser is actuated the upper housing part is rotated relative to the lower housing part, the lower housing part taking the spring housing with it. The spring is thereby compressed and biased by means of the helical thrust gear and the locking mechanism engages automatically. The angle of rotation is preferably a whole-number fraction of 360 degrees, e.g. 180 degrees. At the same time as the spring is biased, the power takeoff part in the upper housing part is moved along by a given distance, the hollow plunger is withdrawn inside the cylinder in the pump housing, as a result of which some of the fluid is sucked out of the storage container and into the high pressure chamber in front of the nozzle.

If desired, a number of exchangeable storage containers which contain the fluid to be atomised may be pushed into the atomiser one after another and used in succession. The storage container contains the aqueous aerosol preparation according to the invention. The atomising process is initiated by pressing gently on the actuating button. As a result, the locking mechanism opens up the path for the power takeoff member. The biased spring pushes the plunger into the cylinder of the pump housing. The fluid leaves the nozzle of the atomiser in atomised form.

Further details of construction are disclosed in PCT Applications WO 97/12683 and WO 97/20590, to which reference is hereby made.

The components of the atomiser (nebuliser) are made of a material which is suitable for its purpose. The housing of the atomiser and, if its operation permits, other parts as well, are preferably made of plastics, e.g. by injection moulding. For medicinal purposes, physiologically safe materials are used.

Figures 6a/b of WO 97/12687, show the nebuliser (Respimat®) which can advantageously be used for inhaling the aqueous aerosol preparations according to the invention.

Figure 6a of WO 97/12687 shows a longitudinal section through the atomiser with the spring biased while Figure 6b of WO 97/12687 shows a longitudinal section through the atomiser with the spring relaxed.

The upper housing part (51) contains the pump housing (52) on the end of which is mounted the holder (53) for the atomiser nozzle. In the holder is the nozzle body (54) and a filter (55). The hollow plunger (57) fixed in the power takeoff flange (56) of the locking mechanism projects partially into the cylinder of the pump housing. At its end the hollow plunger carries the valve body (58). The hollow plunger is sealed off by means of the seal (59). Inside the upper housing part is the stop (60) on which the power takeoff flange abuts when the spring is relaxed. On the power takeoff flange is the stop (61) on which the power takeoff flange abuts when the spring is biased. After the biasing of the spring the locking member (62) moves between the stop (61) and a support (63) in the upper housing part. The actuating button (64) is connected to the locking member. The upper housing part ends in the mouthpiece (65) and is sealed off by means of the protective cover (66) which can be placed thereon.

The spring housing (67) with compression spring (68) is rotatably mounted on the upper housing part by means of the snap-in lugs (69) and rotary bearing. The lower housing part (70) is pushed over the spring housing. Inside the spring housing is the exchangeable storage container (71) for the fluid (72) which is to be atomised. The storage container is sealed off by the stopper (73) through which the hollow plunger projects into the storage container and is immersed at its end in the fluid (supply of active substance solution). The spindle (74) for the mechanical counter is mounted in the covering of the spring housing. At the end of the spindle facing the upper housing part is the drive pinion (75). The slider (76) sits on the spindle.

The nebuliser described above is suitable for nebulising the aerosol preparations according to the invention to produce an aerosol suitable for inhalation.

If the formulation according to the invention is nebulised using the method described above (Respimat®) the quantity delivered should correspond to a defined quantity with a tolerance of not more than 25%, preferably 20% of this amount in at least 97%, preferably at least 98% of all operations of the inhaler (spray actuations). Preferably, between 5 and 30 mg of formulation, most preferably between 5 and 20 mg of formulation are delivered as a defined mass on each actuation.



However, the formulation according to the invention may also be nebulised by means of inhalers other than those described above, e.g. jet stream inhalers or other stationary nebulisers.

5 Accordingly, in a further aspect, the invention relates to pharmaceutical formulations in the form of propellant-free inhalable solutions or suspensions as described above combined with a device suitable for administering these formulations, preferably in conjunction with the Respimat®. Preferably, the invention relates to propellant-free inhalable solutions or suspensions characterised by the combination of active substances 1 and 2 according to the  
10 invention in conjunction with the device known by the name Respimat®. In addition, the present invention relates to the above-mentioned devices for inhalation, preferably the Respimat®, characterised in that they contain the propellant-free inhalable solutions or suspensions according to the invention as described hereinbefore.

According to the invention, inhalable solutions which contain the active substances 1 and 2  
15 in a single preparation are preferred. The term "single preparation" also includes preparations which contain the two ingredients 1 and 2 in two-chamber cartridges, as disclosed for example in WO 00/23037. Reference is hereby made to this publication in its entirety.

20 The propellant-free inhalable solutions or suspensions according to the invention may take the form of concentrates or sterile inhalable solutions or suspensions ready for use, as well as the above-mentioned solutions and suspensions designed for use in a Respimat®. Formulations ready for use may be produced from the concentrates, for example, by the addition of isotonic saline solutions. Sterile formulations ready for use may be  
25 administered using energy-operated free-standing or portable nebulisers which produce inhalable aerosols by means of ultrasound or compressed air by the Venturi principle or other principles.

Accordingly, in another aspect, the present invention relates to pharmaceutical  
30 compositions in the form of propellant-free inhalable solutions or suspensions as described hereinbefore which take the form of concentrates or sterile formulations ready for use, combined with a device suitable for administering these solutions, characterised in that the device is an energy-operated free-standing or portable nebuliser which produces inhalable aerosols by means of ultrasound or compressed air by the Venturi principle or other  
35 methods.

**Examples of Formulations**

The following examples of formulations, which may be obtained analogously to methods known in the art, serve to illustrate the present invention more fully without restricting it to the contents of these examples.

**Inhalable powders:**

1)

<b>Ingredients</b>	<b>µg per capsule</b>
<u>2</u> (hydrochloride)	50
budesonide	200
lactose	4750
<b>Total</b>	5000

10

2)

<b>Ingredients</b>	<b>µg per capsule</b>
<u>2</u> (hydrochloride)	50
Fluticasone-propionate	125
lactose	4825
<b>Total</b>	5000

15 3)

<b>Ingredients</b>	<b>µg per capsule</b>
<u>2</u> (hydrochloride)	50
Mometasone-furoate X H <sub>2</sub> O	250
lactose	4700
<b>Total</b>	5000

4)

Ingredients	$\mu\text{g}$ per capsule
<u>2</u> (hydrochloride)	50
Ciclesonide	250
lactose	4700
<b>Total</b>	5000

5)

Ingredients	$\mu\text{g}$ per capsule
<u>2-en</u> (hydrochloride)	20
budesonide	125
lactose	4855
<b>Total</b>	5000

5 6)

Ingredients	$\mu\text{g}$ per capsule
<u>2-en</u> (hydrochloride)	20
Fluticasone-propionate	200
lactose	4780
<b>Total</b>	5000

7)

Ingredients	$\mu\text{g}$ per capsule
<u>2-en</u> (hydrochloride)	25
Mometasone-furoate X H <sub>2</sub> O	250
lactose	4725
<b>Total</b>	5000

8)

Ingredients	$\mu\text{g}$ per capsule
<u>2-en</u> (hydrochloride)	25
Ciclesonide	250
lactose	4725
<b>Total</b>	5000

9)

Ingredients	$\mu\text{g}$ per capsule
<u>2-en</u> (hydrochloride)	10
budesonide	125
lactose	4865
<b>Total</b>	5000

10)

Ingredients	$\mu\text{g}$ per capsule
<u>2-en</u> (hydrochloride)	10
Fluticasone-propionate	200
lactose	4790
<b>Total</b>	5000

5

11)

Ingredients	$\mu\text{g}$ per capsule
<u>2-en</u> (hydrochloride)	15
Mometasone-furoate X H <sub>2</sub> O	250
lactose	4735
<b>Total</b>	5000

12)

Ingredients	$\mu\text{g}$ per capsule
<u>2-en</u> (hydrochloride)	15
Ciclesonide	250
lactose	4735
<b>Total</b>	5000

B) Propellant-containing aerosols for inhalation:

1)

Ingredients	% by weight
<u>2-en</u> (hydrochloride)	0.01
budesonide	0.4
soya lecithin	0.2
TG 134a : TG227 = 2:3	ad 100

5 2)

Ingredients	% by weight
<u>2-en</u> (hydrochloride)	0.01
Fluticasone-propionate	0.3
Isopropyl myristate	0.1
TG 227	ad 100

3)

Ingredients	% by weight
<u>2-en</u> (hydrochloride)	0.01
Mometasone-furoate X H <sub>2</sub> O	0.6
Isopropyl myristate	0.1
TG 227	ad 100

4)

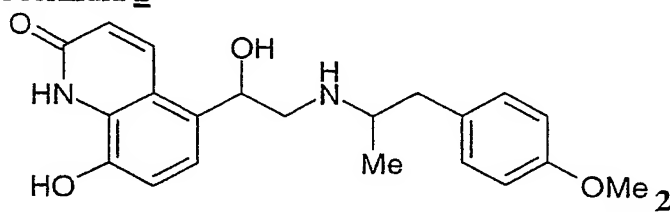
Ingredients	% by weight
<u>2-en</u> (hydrochloride)	0.01
Ciclesonide	0.4
Isopropyl myristate	0.1
TG 134a : TG227 = 2:3	ad 100

10

## Patent Claims

- 1) Pharmaceutical compositions, comprising one or more, preferably one steroid 1, optionally in the form of the enantiomers, mixtures of the enantiomers or in the form of the racemates thereof, optionally in the form of the solvates or hydrates thereof,

and a betamimetic of formula 2

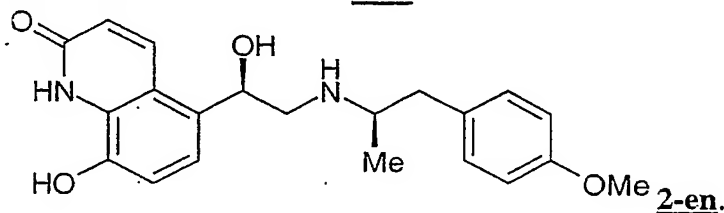


- optionally in the form of its diastereomers, mixtures of its diastereomers, racemats or physiologically acceptable acid addition salts thereof, and optionally in form of the hydrates or solvates thereof,

and optionally together with a pharmaceutically acceptable excipient.

- 2) Pharmaceutical composition according to claim 1, characterised in that the active substances 1 and 2 are present either together in a single formulation or in two separate formulations.

- 3) Pharmaceutical composition according to claim 1 or 2, characterised in that 2 is present in form of its enantiomer of formula 2-en



- 4) Pharmaceutical composition according to claim 1, 2 or 3, characterised in that the pharmaceutically acceptable salts formed by 2 are selected from among the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, 1-hydroxy-2-naphthalenecarboxylic acid, 4-phenylcinnamic acid, maleic acid, or mixtures thereof.

- 5) Pharmaceutical composition according to one of claims 1 to 4, characterised in that the steroids 1 are selected from the group consisting of methyl prednisolone, prednisone, butixocort propionate, RPR-106541, flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide, ST-126, dexamethasone, 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid (S)-fluoromethyl ester, and 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-17 $\alpha$ -propionyloxy-androsta-1,4-diene-17 $\beta$ -carbothioic acid (S)-(2-oxo-tetrahydro-furan-3S-yl) ester.
- 6) Pharmaceutical compositions according to one of claims 1 to 5, characterised in that the compounds 1 are present in the form of salts or derivatives including sodium salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates.
- 7) Pharmaceutical compositions according to one of claims 1 to 6, characterised in that the weight ratios 1 to 2 are in a range from about 1:250 to 250:1, preferably from 1:150 to 150:1.
- 8) Pharmaceutical composition according to one of claims 1 to 7, characterised in that it is in the form of a preparation suitable for inhalation.
- 9) Pharmaceutical composition according to claim 8, characterised in that it is a preparation selected from among the inhalable powders, propellant-containing metered-dose aerosols and propellant-free inhalable solutions.
- 10) Pharmaceutical composition according to claim 9, characterised in that it is an inhalable powder which contains 1 and 2 in admixture with suitable physiologically acceptable excipients selected from among the monosaccharides, disaccharides, oligo- and polysaccharides, polyalcohols, salts, or mixtures of these excipients with one another.
- 11) Inhalable powder according to claim 10, characterised in that the excipient has a maximum average particle size of up to 250 $\mu$ m, preferably between 10 and 150 $\mu$ m.
- 12) Pharmaceutical composition according to claim 9, characterised in that it is an inhalable powder which contains only the active substances 1 and 2 as its ingredients.

13) Pharmaceutical composition according to claim 9, characterised in that it is a propellant-containing inhalable aerosol which contains 1 and 2 in dissolved or dispersed form.

5

14) Propellant-containing inhalable aerosol according to claim 13, characterised in that it contains, as propellant gas, hydrocarbons such as n-propane, n-butane or isobutane or halohydrocarbons such as chlorinated and/or fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane.

10

15) Propellant-containing inhalable aerosol according to claim 14, characterised in that the propellant gas is TG11, TG12, TG134a, TG227 or mixtures thereof, preferably TG134a, TG227 or a mixture thereof.

15

16) Propellant-containing inhalable aerosol according to one of claims 13 to 15, characterised in that it may contain up to 5 % by weight of active substance 1 and/or 2.

20

17) Pharmaceutical composition according to claim 9, characterised in that it is a propellant-free inhalable solution which contains water, ethanol or a mixture of water and ethanol as solvent.

18) Inhalable solution according to claim 17, characterised in that it optionally contains other co-solvents and/or excipients.

25

19) Inhalable solution according to claim 18, characterised in that it contains as co-solvents ingredients which contain hydroxyl groups or other polar groups, e.g. alcohols - particularly isopropyl alcohol, glycols - particularly propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol; polyoxyethylene alcohols and polyoxyethylene fatty acid esters.

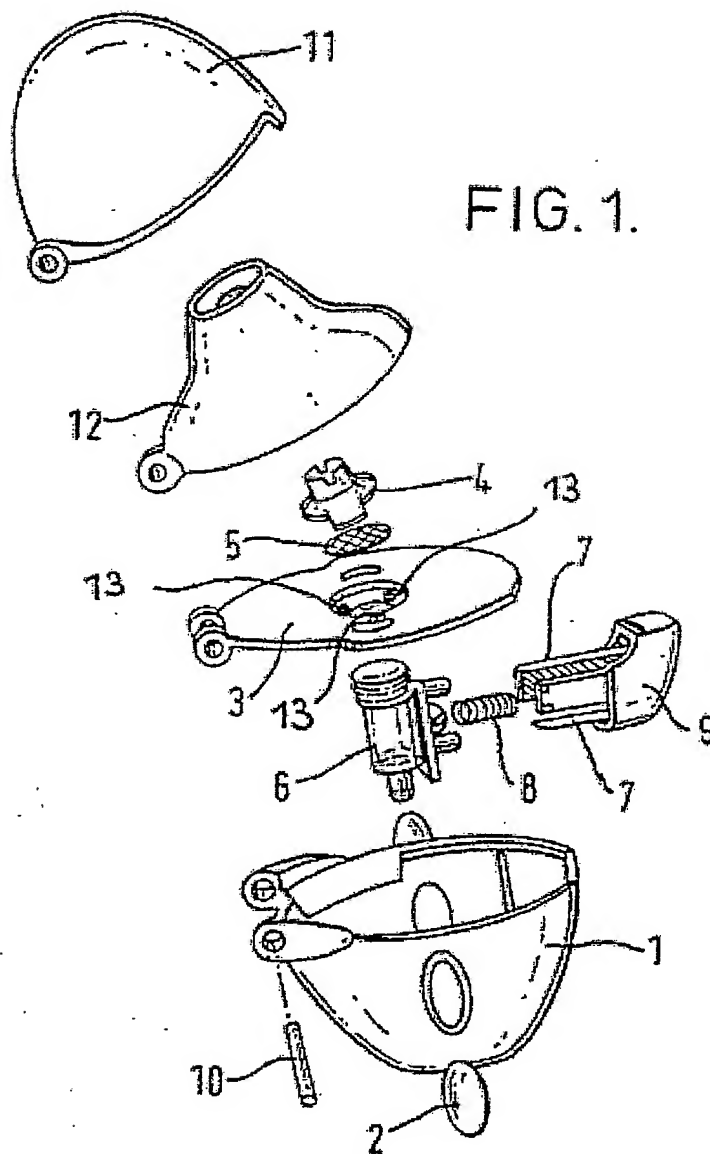
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20) Inhalable solutions according to one of claims 18 or 19, characterised in that they contain as excipients surfactants, stabilisers, complexing agents, antioxidants and/or preservatives, flavourings, pharmacologically acceptable salts and/or vitamins.



- 21) Inhalable solutions according to claim 20, characterised in that they contain as complexing agents editic acid or a salt of editic acid, preferably sodium edetate.
- 22) Use of a composition according to one of claims 1 to 21 for preparing a  
5 medicament for the treatment of inflammatory or obstructive respiratory complaints, particularly asthma or COPD.

1/1



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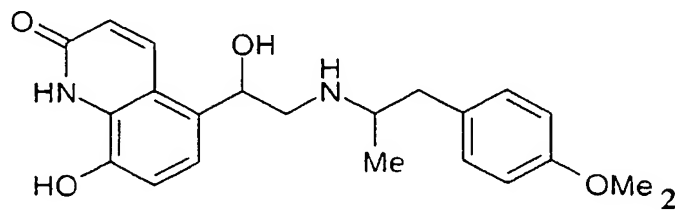
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88447 WARTHAUSEN (DE).

(88) Date of publication of the international search report:  
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*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: **MEDICAMENTS FOR INHALATION COMPRISING STEROIDS AND A BETAMIMETIC**



(57) Abstract: The present invention relates to novel pharmaceutical compositions comprising one or more, preferably one steroid 1 and a betamimetic of Formula (2) processes for preparing them and their use in the treatment of respiratory complaints.

WO 2005/013945 A3

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/008023

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC 7	A61K45/06	A61P11/00 A61P11/06 A61K31/4704 A61K9/12
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the International search (name of data base and, where practical, search terms used)		
EPO-Internal		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	EP 1 452 179 A (CHIESI FARMACEUTICI S.P.A) 1 September 2004 (2004-09-01)  paragraph '0026!; claims 1-13 paragraph '0029!; examples 1-4 paragraphs '0038! - '0045!	1-10, 12-14, 17-19,22
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
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Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  Kanbier, D

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